CHAPTER 23

Melanoma and other skin cancers

Eric H. Jensen, MD, Kim A. Margolin, MD, and Vernon K. Sondak, MD

The skin is the most common site of cancer development in humans. Each year, more than 1 million people are diagnosed with skin cancer. The incidence of all other cancers combined is 1.3 million per year, meaning that skin cancer accounts for nearly 50% of all newly diagnosed cancers.

Melanoma represents approximately 4% of all skin cancers but is responsible for nearly three times the number of deaths as nonmelanoma skin cancers (7,700 vs 2,820). The incidence of melanoma has increased steadily since 1930 and continues to rise at a rate that has exceeded all other cancer types. Melanoma is now the fifth most common cancer in men and the seventh most common cancer in women.

Advances in public awareness, surgical techniques, and adjuvant therapy have improved outcomes for patients with melanoma; however, it remains a highly morbid disease. Because of the relatively young age of onset, the toll of melanoma in terms of "life-years lost" is second only to leukemia among all malignancies in the United States

Epidemiology

Age Melanoma affects a broad range of age groups, including patients in their 20s and 30s, and even younger, with an average age of development of 55 years. Three-quarters of all cases will occur in individuals younger than 70 years of age. Age has been considered by some to be an independent predictor of long-term outcome, with decreasing survival noted in those patients diagnosed over 65 years of age. Paradoxically, however, emerging data suggest that younger patients are more likely to have involvement of regional lymph nodes with early-stage tumors.

Gender Men are slightly more likely to develop melanoma than women (1.2:1.0). Moreover, when compared stage for stage, men have a slightly worse prognosis than women. The most common site affected in men is the trunk, whereas the extremities are most affected in women. In the 25- to 29-year-old female population, melanoma is now the most common malignancy; it is surpassed only by breast cancer in the 30- to 35-year-old range.

Location Many studies have demonstrated that melanomas located on the head/neck, trunk, or back carry a worse prognosis than those on the extremi-

ties. It remains unclear whether that is due to delayed diagnosis of melanomas in more difficult to visualize sites or to an inherently poorer prognosis of melanomas in those sites. On the extremities, acral lentiginous and subungual melanomas carry a poor prognosis, with notably high local recurrence rates. In a small percentage of patients (< 10%), melanoma may arise in noncutaneous locations, including the pigmented cells of the retina and the mucous membranes of the oropharynx, vulva, and anal canal. These primary sites frequently go unnoticed until disseminated disease is present.

Geography Melanoma is most common in parts of the world where fair-skinned whites live in a sunny climate near the equator. Thus, Australia and Israel have among the highest melanoma incidences in the world (approximately 40 per 100,000 individuals per year). Whites in Hawaii and the southwestern United States also have a high incidence of melanoma, about 20-30 cases per 100,000 individuals annually, which equals or exceeds the incidence of colorectal cancer in those regions. The incidence of melanoma in the United States decreases with increasing latitude (ie, more northerly regions); overall, about 12 cases of melanoma are seen per 100,000 American whites.

Race Skin cancer is uncommon in black individuals, with an annual age-adjusted incidence of only 0.9% of that of whites. Asian and Hispanic individuals are similarly at low risk. It is important to recognize, however, that melanoma and other skin cancers do occur in these groups, and suspicious lesions should be appropriately evaluated.

The presentation of skin cancer may differ in blacks as well. For example, most melanomas in these patients occur in the less-pigmented skin of the palms and soles. Also, although basal cell carcinomas are rarely pigmented in fair-skinned individuals, they are almost always pigmented in blacks. Finally, the most common sites of squamous cell cancer in whites are the sun-exposed areas of the head/neck and arms, whereas less-exposed areas such as the legs are more common sites of origin in black patients.

Survival If detected at an early stage, most cutaneous melanomas and virtually all nonmelanoma skin cancers can be cured with surgical excision. The prognosis for patients with lymphatic dissemination decreases significantly, and few patients who develop metastatic disease will survive beyond 5 years.

Etiology and risk factors

All cancers arise through an interaction between environmental and genetic factors. The complex balance of these factors determines the likelihood of cancer development. It has been long recognized that there are environmental factors (most notably ultraviolet [UV] light exposure) that increase the risk of melanoma. Familial patterns of inheritance of dysplastic nevi and melanoma (variously called the B-K mole syndrome, dysplastic nevus syndrome, or familial atypical multiple mole and melanoma syndrome) were recognized in the 1970s. Recently, there has also been significant progress in identifying genetic factors that lead to a predisposition for the development of this disease.

Genetic predisposition Multiple genes have been implicated in the development and progression of melanoma. *CDKN2A* and *CDK4* are susceptibility genes located on chromosome 9p21 and 12q14, which code for protein p16ink4A (inhibitor of cyclin-dependent kinase 4A) and $p14^{ARF}$ (alternate reading frame of the same gene) [in case of *CDKN2A*] and cyclin-dependent kinase 4. Through their interactions with p53, Rb, and cyclins/cyclin-dependent kinases, the products of these genes are essential in the control of the cell cycle, and mutations with loss of function may be associated with melanomagenesis. The gene *p16* in particular plays a vital inhibitory role in maintaining cells at the G1/S interface through interactions with cyclin dependent kinases 4 and 6, which control phosphorylation of the retinoblastoma family of proteins. With uninhibited phosphorylation of RB-1 protein, transcription factor E2F-1 is released, inducing S-phase genes. Therefore, mutations in *CDK* genes produce conditions of uninhibited progression of the cell cycle.

Although *CDKN2A* has been implicated in the development of melanoma, there are clearly multiple other factors involved, including intermittent UV light exposure. Germline mutations in *CDKN2A* have been identified in 40% of familial melanoma pedigrees. Additionally, the penetrance of these mutations has been shown to be highly dependent on geographic locations. Comparison of European, American, and Australian pedigrees reveals mutation penetrance by age 80 of 0.57, 0.7, and 0.91, respectively, indicating the importance of environmental factors in addition to genetic predisposition. Variants in the melanocortin-1 receptor gene may contribute to this environmental influence.

It has also been noted that 60%-90% of melanoma cases contain a mutation in the B-*raf* gene, encoding a serine/threonine kinase involved in the mitogen-activated protein kinase (MAPK) pathway. A single transversion (T1796A) in exon 15 results in a missense mutation (V600E), which accounts for ≥ 85% of B-*raf* mutations. Similarly, the Ras family of genes (N-*ras* in particular) is being investigated for its role in melanomagenesis. The Raf and Ras kinase families act as mediators of intracellular signaling with particular importance in the regulation of cell growth.

The observation that B-*raf*–activating mutations can be found in a significant percentage of benign nevi as well as melanoma cell lines had initially led to the belief that these

The RAS-RAF-MEK-ERK-MAP kinase pathway mediates cell signaling and growth control. The BRAF gene encodes a serine/threonine kinase, which is pivotal to normal cell function. Missense mutations of this gene have been identified in approximately 66% of melanomas, and a single substitution (V600E) represents upward of 80% of these mutations. Although normal cells rely on RAS function for activation of BRAF, V600E mutated cells function independently. Melanomas have been identified with BRAF or RAS mutations, but coexisting mutations have not been identified. It has been found that BRAF mutations are more common in vertical growth-phase melanomas than in horizontal-phase melanomas, leading some researchers to believe that the mutation is most important in the progression, rather than initiation, of melanoma. Recent reports have also indicated that melanomas that arise in areas of sun-exposed skin are much more likely to harbor BRAF mutations but may represent a separate but related pathway to melanoma development (*Davies H, Bignell GR, Cox C, et al: Nature 417:949-954, 2002*).

mutations were likely involved in the initiation of malignancy. More recently, it has been shown that only 10% of radial growth phase melanomas contain mutations, compared with 75% of vertical growth phase melanomas. This finding would indicate that B-*raf* may be more important as a determinant of malignant potential rather than an initiator of malignancy but also highlights the fact that much remains to be learned about the key events in the process of melanoma development.

UV light Melanoma and nonmelanoma skin cancers share a common causative factor—exposure to the UV radiation in sunlight—although the precise mechanism of causation and the types of exposure most likely to cause each disease may vary. Most dangerous is UV-B radiation (wavelength, 290–320 nm), but UV-A radiation (320–400 nm) probably also has carcinogenic potential. Overall, skin cancer incidence rates are increasing, likely both because people spend more time in the sunlight and because the atmosphere's ability to screen out UV radiation has decreased (depletion of the ozone layer).

Chronic vs intermittent exposure Different types of skin cancer are associated with different patterns of sun exposure. Almost all basal cell and squamous cell cancers of the skin occur on chronically exposed areas of skin, such as the head, neck, and hands. There is a clear-cut association between *cumulative* sun exposure and the incidence of these nonmelanoma skin cancers.

On the other hand, exposure to intermittent solar radiation appears to be more important in most cases of melanoma. A number of studies have implicated sun exposure during childhood—particularly blistering sunburns—as a major risk factor. Melanoma is more common in indoor workers than outdoor laborers and occurs most often on parts of the body that are only occasionally exposed to the sun. The one exception to this principle is lentigo maligna melanoma, which occurs most frequently on the head and neck of older individuals with a long history of chronic sun exposure and evidence of actinic skin damage, as is the case for nonmelanoma skin cancer. Melanoma is rare on skin surfaces that are never exposed to the sun (the "bathing suit" or doubly covered areas).

Skin type and hair color Not everyone is at equal risk of developing skin cancer. As previously discussed, blacks are at lower risk than whites. Among whites, melanoma occurs most frequently in fair-skinned, light-haired individuals who sunburn easily and rarely or never tan.

Epidemiologic data demonstrate a difference in the association of sun exposure or dysplastic nevus with melanomas in different primary sites. Thus, primary melanoma of the head and neck origin, particularly lentigo maligna melanoma, is more closely correlated with chronic sun exposure, whereas superficial spreading or nodular melanoma of the trunk is more closely correlated with a large number of nevi *(Whiteman DC, Watt P, Purdie DM, et al: J Natl Cancer Inst 95:806-812, 2003).*

Typical moles Typical or benign moles, also called melanocytic nevi, are small (< 6 mm), round, uniformly tan or brown, and symmetrical. They are generally raised above the skin surface, as opposed to freckles. Patients with many (> 25-50) melanocytic nevi are at increased risk of melanoma; most of these patients are also fair-skinned, light-haired individuals who burn easily and rarely tan.

Atypical moles, also called clinically atypical nevi or dysplastic nevi, are larger (generally > 6 mm), irregularly shaped, and have a pebbly surface. They are usually tan or brown but may have various shades of coloration within them.

At least 5% of the white population of the United States has at least one clinically atypical nevus. Otherwise healthy individuals with at least one clinically atypical nevus have a 6% lifetime risk of developing melanoma. This risk rises to as high as 80% in individuals who also have a family history of melanoma.

Some clinically atypical nevi eventually progress to melanoma. Even if every atypical mole is surgically removed, however, the patient remains at an increased risk of melanoma developing in the rest of the normal skin. Until such time, if ever, that genetic testing identifies those individuals with atypical moles who are at greatest risk of melanoma development, all individuals with clinically atypical nevi should be carefully followed. Close follow-up is particularly important in those with a family history of melanoma.

Actinic keratoses are scaly, rough, erythematous patches that occur in chronically sun-exposed areas; they are both markers for and precursors to nonmelanoma skin cancer development. These lesions may progress to squamous cell cancers or, in some cases, regress spontaneously in response to prolonged avoidance of sun exposure. If few in number, actinic keratoses can be removed or destroyed with liquid nitrogen. For multiple lesions, topical fluorouracil (5-FU) and more recently imiquimod cream have been used successfully.

Burns Squamous cell cancers occasionally arise in burns or other scars. Burn scar cancers (so-called Marjolin's ulcers) may have a more aggressive clinical course than the usual nonmelanoma skin cancer.

Giant congenital nevi Congenital nevi are pigmented lesions actually present at birth, as opposed to developing months or years later. Even among known congenital nevi, however, only the giant (> 20 cm in diameter) congenital nevus, a very rare lesion, is a documented precursor to melanoma. Most melanomas occurring in children younger than 10 years of age arise within these lesions. Whenever the cosmetic result permits, giant congenital nevi should be excised in early childhood. If complete excision is impossible, even with staged procedures, close follow-up is indicated.

Xeroderma pigmentosum, a rare congenital disorder in which patients lack the capacity to repair UV-induced DNA damage, is associated with the development of innumerable melanoma and nonmelanoma skin cancers at an early age.

Immunosuppression or prior hematologic malignancy Nonmelanoma skin cancers and to a much lesser degree melanomas are more common in patients who are immunosuppressed or have had previous hematologic malignancies. Furthermore, the aggressiveness of the skin tumors can be significantly greater in these patients.

TABLE 1: The 'ABCDs' for differentiating early melanomas from benign melanocytic nevi

Feature	Benign mole	Melanoma
Asymmetry	No	Yes
Border irregularity	No	Yes
Color	Uniform, tan/brown	Variegated, black
Diameter	< 6 mm	May be > 6 mm

Diagnosis

Although the vast majority of skin cancers are curable, a substantial number of skin cancer-related deaths occur each year. Since these cancers are visible on the skin, early detection should be the goal in every case.

Early diagnosis of melanoma

Differentiation from benign moles Early melanomas may be differentiated from benign moles by assessing the asymmetry, border irregularity, color, and diameter of the lesions (the so-called ABCDs; Table 1). Other signs of melanoma include itching, bleeding, ulceration, or changes in a preexisting benign mole.

Clinically atypical nevi have some, but not all, of the features of melanoma: They are > 6 mm, asymmetrical, and often show border irregularity. Significantly raised areas or regions of dark brown or black pigmentation in a known atypical nevus suggest the development of melanoma. Biopsy of any suspicious skin lesion should be carried out (see section on "Biopsy techniques"). Patients with too many atypical nevi to excise require careful follow-up with frequent skin examinations.

Periodic total-body skin examinations combined with photographs of any atypical nevi and, most importantly, thorough patient education on the need to watch for changes in existing moles or the development of new lesions are essential components of the management of patients with atypical moles.

Differentiating nonmelanoma skin cancers

Nonmelanoma skin cancers usually are not confused with melanomas, since most (but not all) melanomas are pigmented and most (but not all) nonmelanoma skin cancers are not. Basal and squamous cell cancers may be more difficult to distinguish from one another, but certain features are more characteristic of one type than the other. Basal cell cancers often have a pearly, translucent appearance with a rolled border, whereas squamous cell cancers are often keratinized or ulcerated.

Total-body skin examination

Total-body skin examination is a critical step in the initial evaluation and follow-up of a patient with a melanoma, nonmelanoma skin cancer, or clinically atypical nevus. Because of the common denominator of solar exposure in the causation of skin cancer, patients with one skin cancer are at significant risk of harboring or developing a second or even multiple skin cancers, often of a different histologic type. A complete skin examination is essential for patients with clinically atypical nevi, since they have an increased risk of developing melanoma on their entire skin surface, not just within recognized moles.

Fundamental to a thorough and complete skin examination is a well-lit room, a completely disrobed patient, and a relaxed and unhurried approach. Useful adjuncts in some cases include serial photography, both of individual lesions and whole skin areas, and special techniques of illumination and magnification, such as Wood's lamp ("black light") examination and epiluminescence microscopy (direct application of a magnifying lens to an area of the skin that has had oil applied to minimize reflectance).

Examination of lymph nodes

Lymphatic spread is the most frequently encountered type of dissemination in both melanoma and nonmelanoma skin cancers. The regional lymph nodes should be carefully examined in all skin cancer patients at the time of presentation and at each follow-up visit. Since melanoma may also disseminate hematogenously to any lymph node basin in the body, all accessible node groups should be examined in melanoma patients.

Biopsy techniques

When the decision is made to biopsy a suspicious pigmented or nonpigmented skin lesion, several factors must be taken into consideration. Foremost among them is that the pathologist must receive adequate tissue in good condition to permit assessment of all relevant histologic features. Also critical is that the biopsy should not make subsequent surgical treatment more difficult.

Techniques to avoid Shallow shave biopsies, cryosurgery, or electrodesiccation do not allow for pathologic analysis of margins and depth of invasion and should be avoided.

Complete excision Most clinically suspicious skin lesions are best biopsied by complete excision using local anesthesia, taking a 1- to 2-mm margin of normal skin and including some subcutaneous fat.

Incisional or punch biopsy Unusually large lesions or those situated in cosmetically sensitive areas, such as the face, may be biopsied by incisional or punch biopsy. In these cases, the most abnormal area(s)—generally the most elevated portion(s) of the lesion—should be sampled.

Frozen-section analysis is not routinely employed for the diagnosis of skin lesions.

Biopsy of lymph nodes Palpably enlarged lymph nodes suspected of representing melanoma metastasis are best diagnosed using fine-needle aspiration (FNA). A positive aspiration cytology is grounds for performing a full lymph node dissection. If the cytology is nondiagnostic or negative, or if the node location precludes aspiration, an open biopsy is appropriate; only the enlarged node should be removed, with minimal dissection of the surrounding tissue. In this setting, frozen-section analysis may be employed and a full node dissection carried out during the same procedure.

Techniques for enhancing the detection of microscopic nodal metastases by applying more sensitive assay methods are under investigation. One such assay is the polymerase chain reaction (PCR) for the detection of mRNA sequences for tyrosinase, a protein that is specific for melanocytes. The prognostic and therapeutic implications of detecting micrometastases by these methods are under investigation in trials such as the Sunbelt Melanoma Trial.

Pathology

Histologic types of nonmelanoma skin cancer

Basal cell and squamous cell carcinomas The two most common types of nonmelanoma skin cancer are basal cell carcinoma and squamous cell carcinoma. Bowen's disease is the name given to squamous cell carcinoma in situ involving the skin. Merkel's cell cancer is a rarer, more aggressive skin cancer, which presumably arises from the neuroendocrine cells of the skin.

Cancers arising in the skin appendages (eg, hair follicles, sweat glands) can be adenocarcinomas or apocrine cancers; they are exceedingly rare.

Sarcomas The most common primary sarcoma affecting the skin is dermatofibrosarcoma protuberans. Leiomyosarcoma, angiosarcoma, and malignant fibrous histiocytoma can also arise entirely within the skin.

Histologic types of cutaneous melanoma

Melanomas are classified into one of four subtypes (superficial spreading, nodular, lentigo maligna, and acral lentiginous) based on their clinical and histologic appearance as well as their anatomic location. Melanomas within a given subtype tend to behave similarly. Superficial spreading and nodular melanomas are by far the most frequent, comprising 85% of all melanomas. Melanoma progression is typified by an initial radial growth phase, during which time malignant cells spread horizontally, followed by a vertical growth phase, which is characterized by deep tumor invasion. The time course of radial to vertical growth phase transition appears to be a major variable among the different subtypes of melanoma. Because depth of tumor invasion is critical to prognosis, those tumors with an early transition to vertical growth phase have a worse prognosis than those with a prolonged radial growth phase.

Superficial spreading The defining characteristic of superficial spreading melanoma is an extended radial growth phase. Clinically, they appear flat in their

early stages and may be large with heterogeneous pigmentation. These lesions may often be identified and removed prior to deep invasion and potential lymph node involvement. For these reasons, patients with superficial spreading melanoma can generally expect excellent survival rates.

Nodular Nodular melanomas are raised and often have relatively well-defined borders. Frequently, these lesions are darkly pigmented and may appear blue or black. Nodular melanomas demonstrate an early transition to vertical growth phase; thin lesions are rarely found to be nodular. Rather, most patients with nodular melanomas will present with intermediate or thick primary tumors at the time of diagnosis.

Lentigo maligna Elderly patients with extensive sun exposure are at high risk for lentigo maligna melanoma. These lesions are most common on the scalp and face and can be large and irregular; their removal often involves serious cosmetic considerations. In addition, melanoma in situ is frequently identified beyond the margins of the visible lesion, which adds to the difficulty of its removal.

Acral lentiginous The most common anatomic location for acral lentiginous melanomas is the sole of the feet; they may also be found on the palm or subungual region. In fair-skinned populations, they comprise about 2%-8% of all melanomas, whereas in African Americans, Hispanics, and Asians, they represent 40%-60% of all melanomas. They are often diagnosed at advanced stages, because they may be mistaken for benign entities such as trauma or infection. The treatment for lesions involving digits often requires amputation, whereas wide excision is performed for those on the palms and soles, often posing significant reconstructive challenges. Local recurrence rates are generally higher than for other melanoma subtypes.

Staging and prognosis of melanoma

A great deal of information is available regarding factors that correlate with clinical outcome in patients with melanoma. In the absence of known distant metastatic disease, the most important prognostic factor is regional lymph node involvement. Overall, however, 85% of melanoma patients present with clinically normal lymph nodes. In clinically node-negative patients, most investigators have found the microscopic degree of invasion of the melanoma, or microstaging, to be of critical importance in predicting outcome (Tables 2-4).

Microstaging

Two methods have been described for microscopic staging of primary cutaneous melanomas.

Clark's levels Wallace Clark and associates devised a system to classify melanomas according to the level of invasion relative to histologically defined landmarks in the skin. Although Clark's levels correlate with prognosis (lesions with deeper levels of invasion have a greater propensity for recurrence), the inherent problem with Clark's system is that the thickness of the skin—and hence the distance between the various landmark dermal layers—varies greatly in different parts of the body. Furthermore, except for Clark's level I (mela-

TABLE 2: TNM classification of melanoma

Primary tumor (T)	
Tx	Primary tumor cannot be assessed (eg, shave biopsy or regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	Melanoma ≤ 1.0 mm in thickness, with or without ulceration
T1a	Melanoma ≤ 1.0 mm in thickness and Clark's level II or III, no ulceration
T1b	Melanoma ≤ 1.0 mm in thickness and Clark's level IV or V or with ulceration
T2	Melanoma 1.01-2.0 mm in thickness, with or without ulceration
T2a	Melanoma 1.01-2.0 mm in thickness, no ulceration
T2b	Melanoma 1.01-2.0 mm in thickness, with ulceration
T3	Melanoma 2.01-4.0 mm in thickness, with or without ulceration
T3a	Melanoma 2.01-4.0 mm in thickness, no ulceration
T3b	Melanoma 2.01-4.0 mm in thickness, with ulceration
T4	Melanoma > 4.0 mm in thickness, with or without ulceration
T4a	Melanoma > 4.0 mm in thickness, no ulceration
T4b	Melanoma > 4.0 mm in thickness, with ulceration
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one lymph node
N1a	Clinically occult (microscopic) metastasis
N1b	Clinically apparent (macroscopic) metastasis
N2	Metastasis in two to three regional nodes or intralymphatic regional metastasis without nodal metastases
N2a	Clinically occult (microscopic) metastasis
N2b	Clinically apparent (macroscopic) metastasis
N2c	Satellite or in-transit metastasis without nodal metastasis
N3	Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis or satellite(s) with metastasis in regional node(s)
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis to skin, subcutaneous tissues, or distant lymph nodes
M1b	Metastasis to lungs
M1c	Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH) level

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

TABLE 3: Stage groupings for cutaneous melanoma

Clinical staging[a]				Pathologic staging[b]			
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III[c]	Any T	N1	M0				
		N2					
		N3					
				IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a/b	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					Any T	N3	M0
IV	Any T	Any N	Any M1	IV	Any T	Any N	Any M1

[a]Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases; by convention, it should be used after complete excision of the primary melanoma with *clinical* assessment for regional and distant metastases.

[b]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy, except for pathologic stage 0 or stage IA patients, who may not need pathologic evaluation of their lymph nodes.

[c]There are no stage III subgroups for clinical staging.

Adapted from Balch CM, Buzaid AC, Soong SJ, et al: J Clin Oncol 19:3635–3648, 2001.

noma in situ), there is no scientific rationale for considering these landmarks to be biological barriers to tumor growth. For example, there is no a priori reason to suspect that a lesion that reaches but does not invade the reticular dermis is inherently less aggressive than a similar melanoma that penetrates the reticular dermis in an area where the skin is thinner.

Breslow's thickness An alternative microstaging method, described by Alexander Breslow, obviates some of the problems associated with Clark's levels. In this method, the thickness of the primary tumor is measured from the top of the granular layer of the epidermis to the deepest contiguous tumor cell at the base of the lesion using a micrometer in the microscope eyepiece.

TABLE 4: Five-year survival rates of pathologically staged patients[a, b]

	IA	IB	IIA	IIB	IIC	IIIA	IIIB	IIIC
Ta: Nonulcerated melanoma	T1a 95% –	T2a 89% –	T3a 79% –	T4a 67% –	– – –	N1a N2a 67%	N1b N2b 54%	N3 – 28%
Tb: Ulcerated melanoma	– – – –	T1b 91% – –	T2b 77% – –	T3b 63% – –	T4b 45% – –	– – – –	N1a N2a – 52%	N1b N2b N3 24%

[a] Adapted from Balch CM, et al: Melanoma of the skin, in Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

[b] See Table 2 for staging details. N1 = 1 node; N2 = ≥ 2 nodes; Na = microscopic; Nb = macroscopic.

Many investigators have documented an inverse correlation between Breslow's tumor thickness and survival. More important, several studies have demonstrated that tumor thickness conveys more prognostic information than does Clark's level of invasion. In addition, the measurement of tumor thickness is generally more reproducible and less subjective than is the determination of Clark's level.

Occasionally, Breslow's thickness is impossible to determine and only the Clark's level is available for microstaging, usually because of technical factors related to the performance of the biopsy or the preparation of the histologic specimen. These situations, which inevitably result in the loss of important prognostic information, can be largely avoided by the performance of full-thickness (not shave) biopsies and by careful attention to detail when preparing specimens.

Regional lymph node involvement

In clinically localized disease, lymph node involvement is the strongest prognostic indicator in the staging of melanoma. Patients with nodal involvement at the time of their diagnosis have significantly decreased survival when compared with those who do not, independent of the primary lesion. There is a direct relationship between depth of invasion of the primary lesion and the potential for lymph node involvement. The number of involved lymph nodes is inversely related to long-term survival. Patients with a single lymph node with metastatic disease have a better 5-year survival rate of approximately 60% than those who have multiple nodes (20%-25%). Also, patients with clinically enlarged or matted nodes at the time of diagnosis have a worse prognosis than those with microscopic disease.

Clinical and pathologic staging

TNM staging system The melanoma staging committee of the American Joint Committee on Cancer (AJCC) has recently revised the TNM staging system to

reflect more accurately the impact of statistically significant prognostic factors that were validated on a multi-institution sample of over 17,000 melanoma patients. The new system is shown in Tables 2 and 3.

For stages I and II (node-negative) melanoma, the most important prognostic factors are the Breslow depth (for thin melanomas < 1 mm; the Clark's level of invasion retains some prognostic value) and the presence or absence of ulceration (defined as the absence of an intact epidermis overlying a major portion of the primary melanoma). For stage III disease, the predictive factors are the number of nodes and extent of involvement (microscopic vs macroscopic), as well as the presence of satellite or in-transit deposits.

For patients with stage IV disease (distant metastases), there are few but significant differences in prognosis for disease limited to the skin, for subcutaneous and nodal sites vs visceral sites, and for levels of lactic dehydrogenase (LDH) in the serum.

Some of the most significant changes include new cutoff points for T classification (T1 = ≤ 1.0 mm, T2 = 1.01-2.0 mm, T3 = 2.01-4.0 mm, T4 = > 4 mm), inclusion of ulceration as a factor in T stage (a: no ulceration, b: ulceration), replacement of node size with node number for N stage, inclusion of node size (microscopic vs macroscopic) as a factor in N stage, and inclusion of LDH level as a factor in M stage. When incorporated into new clinical protocols, the new system will undoubtedly improve the value of data from clinical trials in this disease (Table 3).

Other prognostic factors

Age Overall, patients who are ≥ 65 years old have an adjusted survival, which is decreased by 10%-15% relative to their younger counterparts. Although this trend has been demonstrated in numerous studies, whether age is truly an independent predictor of survival remains unclear. A different relationship between age and risk of lymph node involvement, however, is emerging. Data from the prospective Sunbelt Melanoma Trial and retrospective studies reveal that younger patients are significantly more likely to harbor nodal disease than older patients with similar lesions. Age, therefore, deserves consideration in management decisions regarding surgical evaluation of nodal basins.

Gender Although many studies reveal a trend toward improved survival in women compared with men, as an independent predictor of survival; it has frequently not reached statistical significance.

Anatomic location There is a correlation between anatomic location and prognosis of primary melanoma. Those with lesions on the back, upper arms, neck, and scalp (BANS area) have a worse prognosis than those with lesions on the extremities. This may be due to the simple fact that these lesions cannot be evaluated easily by the patient because of their inopportune location rather than a manifestation of true differences in tumor biology. Men are more likely to develop truncal melanomas, whereas women are most likely to develop melanoma on their extremities. Acral lesions carry a worse prognosis than other extremity lesions.

Ulceration The presence of ulceration in a primary melanoma has been recognized as one of the strongest negative predictive factors for long-term survival. Ulceration is defined as the lack of a complete epidermal layer overlying the melanocytic lesion. The presence of ulceration essentially upstages affected patients to the next highest T level. In other words, a patient with 1.1–2-mm melanoma that is ulcerated will carry the same long-term prognosis as a patient with a 2.1–4-mm melanoma that does not have ulceration. The likelihood of finding ulceration is directly related to tumor depth: Patients with thin melanomas (≤ 1 mm) have a 6% rate of ulceration, whereas those with > 4-mm melanomas have a 63% incidence of ulceration. Along with tumor depth, ulceration is integral in determining a patient's long-term prognosis. This realization has led to the adoption of ulceration as a staging criterion in the current AJCC guidelines.

Desmoplastic melanoma Desmoplastic melanomas represent a less common but clinically distinct spindle cell variant of melanoma with dense fibrosis and frequent neurotropism. Clinically, they are raised, firm nodules that are amelanotic in up to 40% of patients, leading to a common delay in diagnosis. Likely because of their neurotropism, these tumors have local recurrence rates as high as 40%, which has led many clinicians to advocate local radiation therapy following excision of these lesions. However, whether desmoplastic melanomas that lack neurotropism are truly at high risk for local recurrence, and whether radiation therapy helps control local recurrence if they are, remains an area of debate.

Additionally, although many of these lesions are deeply invasive at the time of diagnosis, desmoplastic melanomas are less likely to involve regional lymph node basins and more commonly develop distant metastases without lymphatic involvement. This observation should not deter sentinel lymph node biopsy in appropriate patients, as approximately 12% will harbor nodal disease. Despite these seemingly adverse prognostic factors, patients with desmoplastic and neurotropic melanomas tend to have overall survival rates that are slightly favorable compared with other melanomas.

Angiolymphatic invasion Defined as invasion of tumor cells into the wall and/or lumen of vessels or lymphatics of the dermis or deeper structures, angiolymphatic invasion is uncommon in malignant melanoma. However, this finding is clearly associated with more aggressive tumors and signifies likely poor outcomes for these patients. Multiple large studies have shown worsened long-term survival and more frequent lymph node involvement in patients with angioinvasive melanomas. In fact, risk of lymphatic involvement increases as much as threefold, whereas 5-year survival is reduced by as much as 50% when comparing matched patients with and without vascular invasion.

Regression The finding of regression represents host immune response to invasive melanoma. Areas where invasive cells may have once existed are replaced by inflammatory reaction and fibrosis, which may make it impossible to determine the precise depth of the initial lesion histologically. There is continuing debate regarding the prognostic importance of regression; however, many

clinicians believe that thin lesions that show signs of regression should be given higher consideration for surgical nodal staging, given the fact that the initial lesion may have initially been more deeply invasive. Although some studies have observed that regressed lesions have a higher propensity for lymph node metastases than nonregressed primaries of the same thickness, this finding has not been universally shown.

Variable numbers of tumor infiltrating lymphocytes (TILs) are observed in melanoma. Tumors with a high number of TILs should carry an improved prognosis because of the active host response to tumor. In fact, many studies have shown this tendency.

Angiogenesis Studies have found angiogenesis to be an independent factor in long-term survival as well as local recurrence. More commonly identified as increases in tumor depth, angiogenesis is a marker of invasive potential. Deep lesions with ulceration and high mitotic rates are typically associated with angiogenesis, and the combination of all of these factors is associated with poor outcome.

Mitotic rate Mitotic rate is measured as the number of mitotic figures per mm^2. In numerous studies, higher mitotic rates (≥ 1 per mm^2) have been found to be predictive of decreased long-term survival and increased metastatic potential.

Treatment of melanomas

SURGICAL TREATMENT OF CUTANEOUS MELANOMA

Excision of the primary lesion

Margins of excision It was recognized over a century ago that tumor cells could extend within the skin for several centimeters beyond the visible borders of a melanoma, so that the risk of local recurrence relates to the width of normal skin excised around the primary. Only much more recently was it realized that the thickness of the primary tumor influenced the likelihood of contiguous spread and that not all melanomas require the same excision margin. This realization prompted a number of randomized trials to determine the optimal excision margins for melanomas of different Breslow's thicknesses.

Initially, a "one-size-fits-all" approach of taking a 5-cm margin around all cutaneous melanomas was adopted. With such wide margins, skin grafts were required after removal of melanomas on most parts of the body. Melanomas < 1 mm thick had low recurrence rates, however, even when less than the full 5-cm margin was excised.

A randomized trial found that when a 1-cm margin of normal skin was taken around a melanoma < 1 mm thick, the local recurrence rate was exceedingly low (< 1%), and patient survival was just as good as if 3-cm margins were taken. For melanomas 1-2 mm in thickness, patient survival was the same for both margins of excision, but the local recurrence rate was higher with the 1-cm margin (3.3% after 10-year follow-up).

Another randomized trial compared 2- vs 4-cm margins for all cutaneous melanomas between 1 and 4 mm in thickness. In this trial, both local recurrence and survival were the same regardless of whether 2- or 4-cm margins were taken. Skin grafts were less frequent and hospital stays shorter with the narrower margin.

In one recently reported phase III trial, 2-cm margins were compared with 5-cm margins for primaries ≤ 2 mm deep. Again, there was no difference in local or distant relapse rate or overall survival.

Current recommendations Based on these three important studies, it is now possible to make rational recommendations for excision margins for melanoma patients.

- For lesions > 1 mm in thickness, the recommended excision margin is 1 cm.
- For lesions 1-4 mm in thickness, a 2-cm margin is recommended.
- At least a 2-cm margin should be taken for lesions > 4 mm in thickness.

Several facts should be considered regarding these recommendations:

- Regardless of the recommended margin, a histologically negative margin is necessary. Thus, if a 2-cm margin is taken and the pathology report reveals melanoma cells or atypical melanocytic hyperplasia at the margins, further excision is indicated.
- When the anatomic location of the primary precludes excision of the desired margin (eg, on the hands and feet or the face), at least 1 cm should be taken as long as the margins are histologically negative.
- If a minor compromise in excision margin can allow primary closure without a skin graft, it is worthwhile.

Management of regional lymph nodes

Physical examination is the primary screening tool for lymphatic involvement with melanoma. All potentially involved basins should be examined as part of a thorough history and physical examination. Patients who present with clinically negative nodes will have their further evaluation defined by the depth and characteristics of their primary melanoma. Currently, those patients with melanoma having Breslow depth ≥ 1 mm are candidates for surgical evaluation of nodal involvement using sentinel lymph node biopsy (SLNB) techniques. Patients with thinner melanomas may also be candidates for SLNB if adverse prognostic factors are identified in their primary tumor.

Patients who have clinically positive (enlarged) lymph nodes will require evaluation to determine whether the nodes are in fact pathologically positive, in which case complete nodal dissection is indicated. The first step in evaluating palpable nodes is generally FNA. Positive cytology is sufficient to mandate complete nodal dissection. A negative or inadequate sample FNA may be repeated, with image guidance if necessary, or may lead directly to an open node biopsy, followed by complete lymphadenectomy in the event of a positive frozen section or touch-prep cytologic determination of metastasis.

Clinically enlarged nodes Melanoma patients with clinically enlarged nodes and no evidence of distant disease (AJCC stage 3) should undergo complete regional lymphadenectomy. Physical examination may be inaccurate in its prediction of nodal involvement, however, and so other techniques may be utilized to identify positive nodes. FNA of palpable nodes may assist in further decision-making. If positive cytology is identified, a lymphadenectomy should be performed. A negative FNA should not preclude further surgical evaluation. Touch-prep cytology may also be a useful adjunct for intra-operative evaluation of suspicious nodes during SLNB or open biopsy.

The Sunbelt Melanoma Trial is a multicenter prospective randomized trial involving 79 centers and more than 3,600 patients. In an evaluation of 961 patients, logistic regression analysis identified increasing Breslow thickness, ulceration, Clark level > III, and patient age ≤ 60 years as independent predictors for an increased risk of nodal disease. Currently, patients with melanoma ≥ 1 mm in Breslow depth are generally advised to undergo surgical staging of the nodes in conjunction with wide local excision. Selected patients with thin melanomas, < 1mm in depth, may also be candidates for surgical staging of the nodes *(Sondak VK, Taylor JM, Sabel MS, et al: Ann Surg Oncol 11:247-258, 2004).*

Clinically normal nodes The surgical management of clinically normal nodes is determined by the characteristics of the primary lesion. A direct relationship between thickness of the primary lesion and nodal involvement has long been recognized. In addition, the Sunbelt Melanoma Trial has identified additional prognostic factors that increase the risk of nodal disease (see sidebar).

Thin melanomas Patients with thin melanomas (< 1 mm Breslow depth) have a low risk of occult nodal involvement (< 5%) and therefore generally undergo wide excision of their melanoma with 1-cm margins and no nodal staging procedure. Some patients with melanomas 0.76 mm-1 mm have a high enough risk of lymph node involvement to justify consideration of SLNB in addition to wide excision.

Intermediate-thickness melanomas Melanomas 1-4 mm in thickness are associated with an overall risk of occult lymph node involvement of 20%-25%. However, relative risk rises significantly with increasing depth of invasion. Patients with a 1-mm thick melanoma have approximately a 15% chance of involvement, whereas those with a 4-mm melanoma have up to a 55% risk of nodal metastases. For these reasons, 2-cm wide excision of the primary tumor is generally accompanied by SLNB for evaluation of the nodal basin involved. An alternative approach of wide excision alone with observation and serial physical examination of nodal basins has been advocated by some clinicians and has not been shown to reduce long-term survival if complete lymph node dissection is performed at the identification of clinically positive nodes. The use of SLNB vs observation continues to be an area of intense debate.

Selective lymphadenectomy The identification and management of nodal disease have evolved significantly over the past 20 years. The evolution of SLNB has led to an improved ability to accurately stage patients earlier in their disease process. Historically, complete lymph node dissections were performed electively on patients with intermediate and thick melanomas with the belief

that they would lead to a survival benefit. With elective node dissection, however, a significant percentage (80%-85%) of patients underwent complete lymphadenectomy only to find that their nodal basin was free of disease. Prospective, randomized trials failed to confirm a survival benefit for elective node dissection, and so this procedure was largely abandoned in favor of a "watch-and-wait" approach, with therapeutic node dissection performed for those patients who developed subsequent lymphadenopathy.

Currently, node dissection is used selectively, only on those melanoma patients who have been shown to have nodal involvement by SLNB. SLNB was described by Morton et al, who found that dermal injection of vital blue dye (Lymphazurin) surrounding the primary melanoma site allowed for visualization of the draining lymphatics and the "sentinel" node, which was defined to be the first draining lymph node receiving lymph from the primary tumor bed. The original dye-based technique allowed for identification of the "sentinel" node in approximately 85% of cases.

To increase the success rate for sentinel node identification, technetium-99m–labeled sulfur colloid is injected into the primary site preoperatively, and the potentially involved lymph basins are identified with a gamma camera. The patient is then taken to the operating room, where a hand-held gamma probe is used to identify the sentinel node(s). This technique, in combination with the use of vital blue dye, has led to a success rate exceeding 99% in most large current trials.

The ability to accurately detect or rule out disease in the sentinel lymph node has allowed many patients to forego the higher morbidity of complete node dissection. In addition, patients can be more accurately staged and treated earlier in the course of their disease. The intuitive hope that this ability could lend itself to improved survival in patients who undergo SLNB remains to be determined in prospective, randomized trials. Even in the absence of a proven survival benefit, however, the staging advantages of SLNB are sufficiently compelling to justify its routine use in healthy patients with melanomas and a significant risk of nodal involvement. Current data also support the watch-and-wait approach to nodal evaluation, with lymph node dissection (LND) reserved for those who develop clinically positive nodes, which still has a place in the treatment of melanoma and likely does not negatively impact survival. The prospective clinical trials are currently investigating the role of completion lymphadenectomy following positive SLNB.

The evolution of reverse-transcriptase polymerase chain reaction (RT-PCR) has allowed for identification of submicroscopic metastatic nodal disease. It is unknown whether submicroscopic metastatic disease has clinical relevance in the long-term survival of patients with melanoma. These issues are currently being prospectively investigated in the Sunbelt Melanoma trial. Although a number of retrospective studies have suggested that RT-PCR analysis has a role to play in predicting outcome for patients with histologically negative sentinel nodes, a recent study with longer follow-up suggested that this predictive value was lost over time. This observation stresses the importance of prospective evaluation of candidate prognostic tests such as RT-PCR.

Thick melanomas Primary melanomas > 4 mm in thickness are treated with a 2-cm excision margin. In addition, because deep melanomas harbor nodal metastases in up to 60% of patients, surgical evaluation of the nodal basin is generally pursued. Although elective LND has not proven beneficial in these patients, SLNB has been used extensively to guide diagnostic, prognostic, and therapeutic decision-making.

Isolation limb perfusion In-transit metastases—ie, cutaneous or subcutaneous nodules arising between the primary site and the regional lymph node basin—are a well-recognized, but fairly uncommon, site of failure in cutaneous melanoma. A surgical technique developed to treat in-transit metastases, isolation limb perfusion, involves cannulating the artery and vein to an extremity and connecting the cannulas to a cardiopulmonary bypass machine. This technique effectively isolates the blood flow to that extremity and allows for prolonged perfusion with cytotoxic and/or biologic agents.

Most commonly, the chemotherapeutic agent melphalan (Alkeran) has been used for isolation limb perfusion; this drug is generally heated to an elevated temperature (up to 41°C) and perfused for up to 90 minutes. Hyperthermic isolation perfusion with melphalan alone or combined with the investigational agent tumor necrosis factor-α (TNF-α) results in the regression of > 90% of cutaneous in-transit metastases. This approach is useful for limited clinical situations at centers experienced in the technique.

Hyperthermic isolation perfusion with melphalan has also been combined with wide excision in patients at high risk of recurrence of in-transit metastases. Adjuvant use of perfusion demonstrated no significant benefit in a large, international intergroup trial, however, and cannot be recommended.

The current US cooperative group studies for stage III melanoma are divided into low- and high-risk categories for randomized trials of adjuvant therapy. Patients with high-risk disease, defined as stage IIIB or higher (Tables 2 and 3), are randomized to receive 1 year of high-dose IFN-α or three cycles of biochemotherapy containing dacarbazine, cisplatin, vinblastine, IFN-α, and IL-2. Patients with T3 or T4 primary melanoma and up to one microscopically involved node are randomized to receive 1 month of high-dose IFN-α or no systemic adjuvant therapy. The results of both of these studies may prove to raise more questions than are answered. For example, a result favoring biochemotherapy will raise the question of which component is essential for the adjuvant activity (see text and Table 5). A result favoring IFN-α would not definitively answer whether 1 month or 1 year of therapy is optimal for this uniquely selected group of patients.

SURGICAL TREATMENT OF NONCUTANEOUS MELANOMA

Noncutaneous melanomas generally present at a more advanced stage than cutaneous lesions. The site of the lesion greatly affects the approach to the primary tumor and regional lymph nodes.

Ocular melanomas generally do not have access to lymphatic channels, so the surgical principles outlined previously do not apply here. However, the unique propensity to metastasize hematogenously, often to the liver after a long relapse-free interval, warrants further study of this primary site's unique

biology. Advances in understanding the biology of ocular melanomas may lead to adjuvant approaches different from therapies now under investigation for cutaneous primaries.

A diagnosis of ocular melanoma with no evidence of distant disease signifies that a decision must be made as to whether or not the eye can be spared. Some small melanomas situated peripherally in the retina can be excised with minimal loss of vision, but most cannot. For larger lesions, treatment options are enucleation (total removal of the eye) or implanted radiotherapy with a radioactive gold plaque fitted to the back of the eyeball immediately behind the tumor. A multi-institution, randomized trial comparing implanted radiotherapy with enucleation for local disease control and overall survival was completed by the Collaborative Ocular Melanoma Study Group; it appears that both techniques provide similar outcomes for all sizes of tumor.

Melanomas of the anus and vulva pose challenges in the treatment of both the primary lesion and regional nodes. Excision of primary tumors in these areas should not be overly radical: Abdominoperineal resection or radical vulvectomy is unnecessarily deforming and is not associated with improved survival compared with wide local excision. Abdominoperineal resection, with its attendant permanent colostomy, is indicated only for locally recurrent melanomas after prior sphincter-conserving excision or for melanomas with radiographic evidence of mesorectal node involvement.

Anal and vulvar melanomas often present with inguinal lymph node metastases; if there is no evidence of distant disease, both the primary site and regional nodes should be removed.

Nasal sinuses or nasopharyngeal melanomas Melanomas arising in the nasal or nasopharyngeal mucosa should be widely excised to include adjacent bony structures, if needed. Node dissection is reserved for patients who have proven nodal involvement. Radiation therapy should be considered for those patients whose primary tumor cannot be fully removed from this site with adequate margins.

ADJUVANT THERAPY FOR MELANOMA

The 10-year disease-free survival estimate for patients with T1a (≤ 1 mm deep) and T1b (1.01-2 mm deep) is approximately 85%. However, fewer than half of patients with deep primaries or intermediate-level primaries with ulceration (see new proposed AJCC system) and/or regional lymph node involvement will experience long-term disease-free survival.

Development of adjuvant therapy approaches that increase survival over surgery alone has been a long-standing goal of melanoma researchers.

Interferon-α-2b (IFN-α-2b) and adjuvant therapy for stage III melanoma

The epoch of effective adjuvant therapy for resected high-risk melanoma began with the publication of Eastern Cooperative Oncology Group (ECOG) protocol 1684 in 1996, which demonstrated a survival benefit associated with the administration of 1 year of "high-dose" IFN-α, consisting of 4 weeks of

treatment, 5 days per week, at 20 mU/m^2 IV followed by 11 months of treatment, 3 times per week, at 10 mU/m^2 SC. The results of this practice-altering trial led to the approval of this drug for melanoma and to its established role as the comparator arm in several subsequent phase III adjuvant trials. The two subsequent large US cooperative group trials for high-risk resected local and regional melanoma confirmed the activity of high-dose IFN-α and the lack of benefit for less aggressive IFN-α regimens as well as for a ganglioside vaccine that had shown promise in this setting. Nearly all of the other trials, both before and after ECOG 1684 and predominantly in European centers, consisted of lower-dose, more prolonged administration of IFN-α. These regimens, although appearing to delay relapse in some cases, offered no survival benefit and have not been recommended for use outside clinical trials.

The most recent study is a multi-institution, randomized trial of polyethylene glycol IFN-α, a chemically modified molecule designed to prolong the exposure and decrease the frequency of administration. Although this agent is active for diseases that are responsive to low-dose IFN-α, such as chronic viral hepatitis and chronic myelogenous leukemia, it is not likely to prove beneficial for the adjuvant therapy of melanoma unless the chemical modification leads to beneficial alterations in the immunologic activity of the IFN-α. Even the role of high-dose IFN-α as a standard therapy or as a comparator for phase III trials has been questioned, since long-term follow-up of the original ECOG data suggests a gradual loss of the benefit over time. One approach currently under investigation is to use high-dose IFN-α as the platform upon which to build multiagent regimens for testing in the adjuvant setting; another approach is to use this agent as part of a vaccine strategy, as detailed later in this chapter.

The toxicities of IFN-α-2b (Intron A) are predominantly constitutional, consisting of fever and chills (which subside in most patients after the first few doses), nausea and anorexia, myalgias, and arthralgias. Fatigue, which may be progressive as therapy continues, is generally the most troublesome side effect and is often dose-limiting. CNS toxicity, ranging from mild difficulties with concentration to severe depression, is also related to the dose and duration of therapy.

The most common laboratory abnormalities consist of asymptomatic elevations in serum levels of transaminase and mild myelosuppression, as well as occasional nephrotoxicity. Virtually all of these effects are reversible and occur in dose- and schedule-dependent patterns.

Optimal adjuvant treatment of node-negative melanoma The best adjuvant intervention for patients with intermediate-risk melanoma has not yet been identified, but the goal of avoiding toxicity and the recognition that these patients may be the ideal candidates for immunotherapeutic interventions have justified the enrollment of these patients in trials of vaccines and low-dose IFN-α-2b. Several trials outside the United States failed to demonstrate a survival benefit using IFN-α-2b in various schedules and doses for patients with high-risk node-negative disease.

Southwest Oncology Group (SWOG) 9035 was an investigation of the adjuvant benefit of Melacine, an allogeneic cell lysate-based vaccine. Melacine had

been shown to have modest activity against advanced melanoma. Although the final results of this study failed to demonstrate a survival benefit for Melacine as administered in this trial, a subset analysis of the impact of HLA class I type was performed as part of the trial, based on observations in the advanced-disease setting suggesting an important interaction between HLA type and vaccine benefit. Eighty percent of the patients in SWOG 9035 had HLA typing performed. When the outcomes of therapy were reevaluated with respect to HLA type and study treatment, a large, statistically significant difference favoring HLA A2 and C3–the same types that appeared to benefit from vaccine treatment for advanced disease–was seen. Because patients were not prestratified by HLA type, this intriguing result, which points to the importance of immunogenetics in the rational design of immunotherapy regimens, will need to be corroborated with a trial designed to test the more precise hypothesis both clinically and with appropriate immunologic correlative studies.

Radiation therapy

Radiation therapy is rarely employed after surgery for primary or nodal melanoma, although recent reports have demonstrated that the pessimistic impression that melanoma is a "nonradioresponsive" tumor is not justified. A study at M. D. Anderson Cancer Center suggested that postoperative radiation therapy to the neck after radical or modified radical neck dissection decreased regional recurrence rates in node-positive patients.

Formal investigation of the role for adjuvant irradiation in patients thought to be at uniquely high risk from locoregional disease has been hampered by technical challenges to protocol design and changes in the practical approach to these patients. Nevertheless, it seems reasonable to consider the use of postoperative radiation therapy in patients with multiple (≥ 10) involved lymph nodes or gross extracapsular extension, as these patients are at high risk of regional recurrence despite adequate lymph node dissection.

Since these patients are also candidates for IFN-α-2b or investigational studies of adjuvant therapy, the optimal schedule for integrating radiation therapy with IFN-α-2b will need to be determined. In the absence of definitive data, we defer the start of radiation therapy until after the completion of the initial month of IV IFN-α-2b.

TREATMENT OF ADVANCED MELANOMA

Chemotherapy

Single agents Among the numerous available chemotherapeutic agents, only dacarbazine (DTIC-Dome), which has an 8%-10% objective response rate when given alone, is currently approved for the treatment of advanced melanoma. Most combination regimens in current use or under investigation include this agent. Temozolomide (Temodar) is an oral alkylating agent approved for the treatment of malignant gliomas that has activity comparable to that of dacarbazine in advanced melanoma. Its mechanism of action is similar to that of dacarbazine, but its high oral bioavailability and penetration into the CNS

make it ideal for consideration in treatment of this disease, with a high propensity for CNS metastasis. Although there are no adequate phase III data supporting this hypothesis, temozolomide has been substituted for dacarbazine in many combination regimens and is currently under investigation in combination with radiation therapy for patients with melanoma metastatic to the brain.

One important mechanism of resistance to dacarbazine and temozolomide is the removal of the chemotherapy-donated alkyl group from its target site on the guanine molecule by the enzyme alkyl guanyl transferase (ATase). Attempts to overcome this form of resistance involve the use of an inhibitor of ATase, O-6-benzyl guanine, or alternative administration schedules that downregulate cellular levels of ATase. Unfortunately, neither of these methods has proven effective so far, and the need remains acute for better cytotoxic agents and a greater understanding of potential targets for new drugs.

A number of other drugs have shown activity in early studies but have not been subjected to the rigorous testing required to define their possible role in current regimens. Thus, older regimens commonly included a nitrosourea, cisplatin, and a vinca alkaloid. More recently, the taxanes have been shown to possess some activity, supporting the development of potentially synergistic regimens with cisplatin. However, in view of their myelosuppression and the requirement for glucocorticoid prophylaxis which could interfere with potential immunochemotherapeutic synergy, the taxanes have not been adopted for widespread use in melanoma.

Combination regimens The principles of combination chemotherapy and potential drug synergy have been applied with limited success to the treatment of advanced melanoma (Table 5). Combinations based on the agents previously listed became popular when the group at M. D. Anderson Cancer Center demonstrated an encouraging response rate in the 40% range for a regimen containing dacarbazine, vinblastine, and cisplatin. When moderate doses of IFN-α and interleukin-2 (IL-2, aldesleukin, Proleukin) were added to this drug combination and given simultaneously, the overall objective response rates exceeded 50%, and complete responses occurred in 10% of patients. In a phase III study from the same institution, a small survival benefit of biochemotherapy over the same chemotherapeutic agents without IFN and IL-2 was achieved.

However, the attempt to reproduce these results in large, randomized cooperative group studies was disappointing, and the addition of the biologic agents was recently shown not to enhance the overall objective response rate and disease progression-free or overall survival. Similarly, disappointing results have been reported in other studies addressed at a similar question, as shown in Table 5. Thus, the role of biochemotherapy in advanced melanoma has not been defined and is not routinely recommended for use outside investigational trials. However, for young, otherwise healthy patients, particularly those who are symptomatic, biochemotherapy may be appropriate for the goal of achieving the highest likelihood of an initial response and symptom relief but rarely provides durable complete remission.

TABLE 5: Randomized trials of biochemotherapy regimens in patients with metastatic melanoma

Regimen	No. of patients	No. of CRs	No. of PRs	OR rate (%)	Median survival (mo)
Falkson study					
DTIC	69	2	8	15	10
DTIC + IFN-α	68	6	8	21	9
DTIC + Tam	68	2	10	18	8
DTIC + IFN-α + Tam	66	3	10	19	10
Rosenberg study					
CDDP + DTIC + Tam	52	8	19	27	16
CDDP + DTIC + Tam + IFN-α ± IL-2	50	6	38	44	11
Ridolfi study					
CDDP + DTIC ± BiCNU	89	3	15	20	9.5
CDDP + DTIC ± BiCNU + IL-2 + IFN-α	87	3	19	25	11
Eton study					
CDDP + DTIC + Vlb	92	1	22	23	9.5
CDDP + DTIC + Vlb + IL-2 + IFN-α	91	6	38	44	11.8
Atkins study					
CDDP + Vlb + DTIC	201	6	17	11	8.7
CDDP + Vlb + DTIC + IL-2 + IFN	204	3	32	17	8.4
Del Vecchio study					
CDDP + Vnd + DTIC	69	0	15	21	12
CDDP + Vnd + IL-2 + IFN	70	2	18	27	11
Keilholz study					
DTIC + CDDP + IFN	180	7	34	23	9
DTIC + CDDP + IFN + IL-2	183	6	32	21	9

BiCNU = carmustine; CDDP = cisplatin; CR = complete response; DTIC = dacarbazine; IFN-α = interferon-α; IL-2 = interleukin-2; OR = overall response; PR = partial response; Tam = tamoxifen; Vlb= vinblastine; Vnd=vindesine

Biological therapies

IFN-α has been evaluated as a single agent in melanoma, and most of its experience is from older studies in which the methods of response assessment and confirmation of outcomes were less rigorous than in current studies. Although initial studies of IFN-α plus single or multiagent chemotherapy suggested activity superior to that expected from the single agents, randomized trials did not show a benefit. Thus, with the exception of its possible use in IL-2–containing biochemotherapy, IFN-α is not currently recommended as a single agent or in combination with available chemotherapy agents in advanced melanoma. It is likely that increased understanding of the biology and immunology of melanoma and the tumor milieu will lead to the inclusion

of IFN-α in new combinations, doses, and schedules for which there is a precise rationale for its use. The most valuable combinations of IFN-α for melanoma are likely to be in the adjuvant setting in carefully sequenced combinations with other immunotherapeutic agents such as peptide vaccine.

IL-2 is the only other recombinant biological molecule with demonstrated antitumor activity against melanoma. The majority of published data come from trials of high doses of IL-2 (600,000-720,000 IU/kg IV every 8 hours for 14 doses, repeated after a 9-day rest period) given over limited treatment durations at toxicity levels requiring inpatient management. The most common toxicities, including hypotension with fluid retention, acidosis and renal insufficiency, neurotoxicity, and cardiovascular complications, can be life-threatening. Mucocutaneous and constitutional toxicities including fever/chills, nausea/anorexia, and profound fatigue may also limit the number of doses tolerated by patients. The generalized capillary leak syndrome may lead to multiorgan dysfunction that requires skill and experience to administer the maximum number of doses tolerated while avoiding life-threatening toxicities. At these dose-intensity levels, objective response rates of approximately 20% have been achieved, with about half of responding patients experiencing durable complete remissions lasting in excess of 5 years. Based on these favorable results, high-dose IL-2 was approved by the FDA in 1998 for the treatment of metastatic melanoma. Recently completed phase III trials have failed to demonstrate a significant reduction in toxicities or enhancement in the therapeutic efficacy of IL-2 using modulators chosen for their selective inhibitory effects on inflammatory pathways associated with the toxic effects of IL-2.

Although the frequency of durable complete responses to IL-2 therapy appears to be

Melanomas often harbor a constitutively activating mutation in B-*raf* kinase, a signaling molecule involved in cell proliferation and survival. Sorafenib (also known as Bay 43-9006) is an investigational oral agent that inhibits the activity of this enzyme as well as that of other signaling molecules, including the receptor for vascular endothelial growth factor, suggesting it may have anti-angiogenic potential as well as direct antitumor activity. Although the single-agent activity of sorafenib was low among previously treated melanoma patients in a phase I trial (*Ahmad T, Marais R, Pyle L, et al: Proc Am Soc Clin Oncol [abstract] 23:708, 2004*), a combination of this agent with carboplatin and paclitaxel provided an objective response rate in the range of 30%, even in previously treated patients (*Flaherty KT, Brose M, Schuchter L, et al: Proc Am Soc Clin Oncol [abstract] 23:708, 2004*). A phase III trial of this combination with or without sorafenib is now under way.

The use of thalidomide as an immunomodulator and/or inhibitor of angiogenesis has been studied extensively in melanoma, but the role for this agent remains undefined. Although initial trials suggested a remarkable level of activity for the combination of temozolomide with thalidomide, phase III trials to define the role of thalidomide remain to be completed. Although the appeal of an all-oral, fairly well-tolerated regimen supports the further development of this combination, the toxicities, particularly the increased risk of thromboembolic events, will require further study. It is possible that related drugs with less toxicity, such as the investigational agent lenalidomide (CC-5013), will have promising activity in melanoma and a more favorable therapeutic ratio (*Bartlett JB, Michael A, Clarke IA, et al: Br J Cancer 90:955-961, 2004*).

higher than that reported for other single agents and combination regimens, it is important to consider that patients selected for their ability to tolerate the serious multisystem toxicities of high-dose IL-2 may represent a more favorable group with a higher a priori likelihood of tumor response. Only limited data are available on the activity of outpatient, low-dose IL-2 regimens in patients with melanoma, and this form of therapy is not recommended outside a clinical trial.

IFN-α-2b plus IL-2 IFN-α-2b and IL-2 have been used together in the treatment of advanced melanoma, as well as other tumors. In addition to potential synergistic antitumor efficacy, the clinical advantage of this combination includes the relative lack of overlapping toxicities. Combinations of IFN-α-2b and IL-2 at maximum doses in either the inpatient or outpatient setting have not, however, achieved a higher response rate than either agent alone in patients with metastatic melanoma and are not recommended for routine use.

Melanoma vaccines Vaccines produced from allogeneic melanoma cell lines administered with one of several available nonspecific immunologic "adjuvants" (which stimulate antigen-presenting cells and enhance other aspects of immune recognition of antigens) have shown limited antitumor activity (generally ≤ 10% objective response rates in patients with limited metastatic disease). Examples include the Melacine data detailed earlier in this chapter and the investigation of Canvaxin, a vaccine produced from two melanoma cell lines and administered with the bacille Calmette-Guerin (BCG) vaccine immune adjuvant. Results of recently completed phase III trials of Canvaxin plus BCG vs BCG as the control for patients with resected stage III or IV melanoma will define the potential role of this form of immunotherapy in the management of patients with resected melanoma at high risk of relapse.

Tumor-specific antigens most critical to mediating an antimelanoma immune response and the relative efficacy of T-cell response vs humoral immune responses remain the subject of ongoing investigations. Peptide vaccines that induce T-cell immunity to precisely defined immunodominant peptides contained in melanoma protein antigens have been developed and in some cases, modified to enhance their presentation by HLA molecules on antigen-presenting cells and recognition by T lymphocytes. These vaccines may work well when administered directly to patients with an immune adjuvant, such as previously described, or may have enhanced immunostimulatory activity when administered as part of a dendritic cell vaccine. Dendritic cell-targeted therapy takes advantage of the dendritic cells' antigen-presenting function, involved in T-cell responses.

Under investigation are peptides from several known melanoma antigens, including the MAGE series, gp-100, tyrosinase, MART-1/Melan-A, and NY-ESO-1. Current studies are directed at the optimization of conditions for the production and administration of dendritic cells in addition to the source and delivery of tumor antigen. Phase III trials are ongoing to study the best immunologic adjuvant as well as combinations of peptide vaccines with cytokines (eg, GM-CSF [granulocyte-macrophage colony-stimulating factor, sargramostim, Leukine] and IL-2) that also enhance the T-cell response.

Gene therapy New advances in gene therapy have made possible the genetic modification of tumor cells as well as effector cells, such as dendritic cells and T cells. Some of the genetic modifications that have been studied include the transfection of genes for immunostimulatory cytokines, allogeneic HLA sequences, and accessory molecules critical for immune recognition. Continued efforts in this area will soon define the optimal system for the application of these laboratory techniques to the immunotherapy for human melanoma.

The effects of GM-CSF and IFN-α as vaccine adjuvants in combination with HLA-A2 peptides from Melan-A/MART-1, gp-100, and tyrosinase in HLA-A2—positive patients with advanced melanoma have been analyzed (*Kirkwood JM, Lee S, Land S, et al: Proc Am Soc Clin Oncol [abstract] 23:707, 2004*). The results suggested an association between immune responses and longer survival, but the potential benefit of peptide vaccine and GM-CSF in the adjuvant setting awaits the results of ECOG 4697, a trial designed for patients with metastatic melanoma that can be fully excised.

Treatment of CNS metastasis

Radiation therapy is the only treatment available for most patients with unresectable brain metastases, but meaningful responses are observed in less than 25% of treated patients. Alternative fractionation schedules have been investigated but have not proved to be superior to standard regimens of whole-brain irradiation. Recently, techniques of stereotactic radiosurgery have shown encouraging results in patients with melanoma metastatic to the CNS; this approach is currently recommended when the size, number, and location of metastases are amenable to stereotactic techniques. The median survival is only a few months. Corticosteroids are often given concomitantly with brain irradiation to minimize intracranial swelling and are tapered off rapidly after the completion of therapy. Because melanoma has limited responsiveness to radiotherapy and is often associated with intracranial hemorrhage, excision should be considered for brain metastases that can be removed safely.

A promising area of vaccine investigation involves the use of CTLA4-Ab, a blocking antibody that inhibits the negative signals transmitted to T cells in the normal control of the immune response. Preliminary data in advanced melanoma patients suggest that this antibody, alone or in combination immunotherapy strategies, may "break immune tolerance," allowing the emergence of a beneficial immune response to tumor. Autoimmune complications of this therapy provide "proof of concept" for this approach but require further study before this form of therapy can be used in the clinic (*Sanderson K, Scotland F, Lee P, et al: J Clin Oncol 23:741-750, 2005; Hersh EM, Weber J, Powderly J, et al: Proc Am Soc Clin Oncol [abstract] 23:709, 2004*).

Attempts to take advantage of systemic therapy using agents that cross the blood-brain barrier, such as the nitrosoureas and temozolomide, have been largely unsuccessful in the treatment of established CNS metastases; their role in the prevention of CNS metastases in patients with extracranial metastatic melanoma is currently under investigation. Nevertheless, they remain in use at centers exploring variations in the chemotherapeutic and/or biologic elements of the regimen.

Radiation therapy is occasionally of benefit in the palliative treatment of melanoma metastatic to bone or other symptomatic sites.

The Cytokine Working Group has evaluated the use of temozolomide with whole-brain irradiation in patients with brain metastases from melanoma *(Margolin K, Atkins B, Thompson A, et al: J Cancer Res Clin Oncol 128:214-218, 2002)*. This regimen was associated with a disappointing 10% objective response rate when rigorous neurologic and radiographic criteria were used to assess the activity of the regimen. Nevertheless, it was well tolerated, and the group has now initiated a trial in which the addition of thalidomide to the temozolomide plus whole-brain irradiation regimen is under investigation. This strategy was based in part on the encouraging results of small phase II studies of temozolomide and thalidomide in patients with metastatic melanoma without brain metastases *(Hwu W-J, Krown SE, Menall JH, et al: J Clin Oncol 21:3351-3356, 2003)*. Early results will be presented at the 2005 American Society of Clinical Oncology annual meeting.

Treatment of nonmelanoma skin cancer

Surgery

Margins of excision Most nonmelanoma skin cancers can be conservatively excised with much narrower margins than are required for cutaneous melanomas. Excision margins of 0.5-1.0 cm are adequate for most nonrecurrent basal cell and squamous cell cancers and yield local recurrence rates under 5%, provided that histologically negative margins are achieved. For most tumors in most anatomic sites, these excision margins can be achieved using standard surgical techniques with local anesthesia and primary closure.

Recurrent cancers and lesions in difficult sites More sophisticated techniques are required for recurrent skin cancers or those in cosmetically difficult areas, such as the tip of the nose or the eyelids. For these lesions, a variation of Mohs' micrographic surgery is frequently employed. Simply stated, this type of surgery is a controlled surgical excision in which the removed tissue is precisely oriented and carefully examined histologically, and serial re-excisions are performed wherever residual disease is noted.

Although Mohs' surgery may take much longer than routine surgical excision, the extra precision can be helpful for identifying the often asymmetrical extensions of skin cancers, thus minimizing the amount of normal tissue resected. After Mohs' surgery has achieved complete excision, reconstruction is performed by whatever means is appropriate but often involves skin grafts or local flaps rather than primary closure.

More aggressive histologic types of skin cancers, particularly Merkel's cell cancers and sarcomas, generally require wider excision than do the more common basal cell and squamous cell cancers. Margins of 2-3 cm are usually taken, similar to those for a thick melanoma. In particular, dermatofibrosarcoma protuberans may spread in an eccentric fashion, with little extension in one direction but many centimeters of subclinical tumor growth in another. Careful examination of the histologic status of the margins is essential. Mohs' surgery may be useful in some cases.

Radiation therapy

Radiation therapy is a potential treatment for skin cancers located in critical sites where surgical excision would be disfiguring. Primary basal cell and squamous cell cancers treated with radiation therapy have nearly identical cure rates (about 95%) to those treated with surgical excision.

Radiation therapy is also employed postoperatively to reduce local recurrence rates after excision of high-grade or recurrent sarcomas of the skin. It can also be used postoperatively in patients with basal cell or squamous cell carcinoma when margins are positive.

Topical and intralesional therapy

Topical therapy Occasionally, patients present with numerous skin cancers or tumors in essentially sensitive areas that would be impossible to resect completely. This scenario is particularly common in the immunosuppressed patient who is predisposed to skin cancer development. For these patients, topical therapy with 5-FU or imiquimod cream can dramatically reduce the number of excisions required.

Direct intralesional injection of IFN-α-2b has been reported to treat basal cell cancers successfully. This technique may be particularly helpful for locally recurrent lesions after surgery and/or radiation therapy.

MANAGEMENT OF RECURRENT DISEASE

Local recurrence The vast majority of nonmelanoma skin cancers are successfully treated with surgery or primary irradiation, with fewer than 5% recurring locally. Of those that do recur locally, at least 80% are cured by further local treatment. Regional lymph node metastases develop in about 5% of patients with squamous cell cancers and ≤ 1% of patients with basal cell cancers. Nodal metastasis is somewhat more common in Merkel's cell cancers but is very unusual in sarcomas of the skin.

Regardless of the histologic type, whenever clinically obvious nodal enlargement occurs, a needle biopsy should be performed and a therapeutic lymph node dissection performed if regional spread is documented. There is essentially no role for elective dissections of clinically normal nodes in any form of nonmelanoma skin cancer.

Distant metastasis occurs in about 2% of patients with squamous cell cancers and 0.1% of patients with basal cell cancers, most frequently after nodal recurrence. No effective therapy exists for metastatic nonmelanoma skin cancer, although a few reports of scattered temporary responses to chemotherapy exist. Lippman and colleagues described encouraging results with the combination of IFN-α and 13-*cis*-retinoic acid (isotretinoin [Accutane]).

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